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09/733,692	12/08/2000	Brian R. Murphy	15280404100	3239

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EXAMINER	
BROWN, STACY S	
ART UNIT	PAPER NUMBER
1648	14

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/733,692	Applicant(s) MURPHY ET AL.	
	Examiner Stacy S Brown	Art Unit 1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *May 15, 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-179* is/are pending in the application.

4a) Of the above claim(s) *99-121 and 138-179* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-98 and 122-137* is/are rejected.

7)☒ Claim(s) *13,43 and 54* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to **Group Art Unit 1648.**

2. Applicant's election of Group I, claims 1-98 and 122-137 is acknowledged. Claims 1-179 are pending. Claims 99-121 and 138-179 are withdrawn from consideration being drawn to non-elected inventions. Applicant is reminded to cancel non-elected claims. Claims 1-98 and 122-137 are examined.

Specification

3. The abstract of the disclosure is objected to because it exceeds the maximum limit of 150 words. See MPEP § 608.01(b).

Claim Objections

4. Claims 13, 43 and 54 are objected to because of the following informalities:

- Claims 13 and 43, missing a period.
- Claim 54, "rB/HPIV3.1F,2HN" has a comma. It is not found in the specification.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 38 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a chimeric PIV containing antigens from one to four pathogens, does not reasonably provide enablement for *protective* antigens. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

"Protective" implies that an infection or disease is prevented. The breadth of the claim encompasses a protective effect against PIV and any other pathogen incorporated into the PIV genome. A variety of pathogens are listed in claim 43 for example, including RSV and HIV, for which there are currently no known preventative antigens. Walker *et al* (*Nature* 407:313-314, 2000) says that single amino-acid changes in an HIV peptide can prevent the peptide from being presented to CTLs. Barouch *et al* (*Nature* 415:335-339, 2002) supports Walker by showing a single nucleotide mutation within an immunodominant Gag CTL epitope that caused an increase in viral replication, leading to a test animal's death (abstract). Barouch demonstrates that protective antigens for HIV are unpredictable. Applicants have not provided guidance for overcoming the unpredictability of preventing HIV, nor shown working examples.

Therefore, the scope of the claims is not enabled. Suggested language for claim 38 is "immunogen" instead of "protective antigen".

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21, 32-41, 97 and 98 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Claim 21, improper Markush language.
- Claim 32-41, "supernumerary" lacks comparative basis.
- Claim 97, the limitation "virus" is redundant.
- Claim 98, it is unclear how the parainfluenza virus is a "subviral particle".

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The following are <u>provisional</u> obviousness-type double patenting rejections because the conflicting claims have not in fact been patented.

- Claims 1-98 and 122-137 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-67 of copending Application No. <u>09/586,479</u>. Although the conflicting claims

are not identical, they are not patentably distinct from each other because the claims of 09/586,479 are drawn to a species of the genus of the instant claims.

- Claims 1-24, 32-34, 38-39, 82-88, 95-98 and 122-137 provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-30 and 46-55 of copending Application No. 09/459,062. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of 09/459,062 are drawn to a species of the genus of the instant claims.

- Claims 1-24, 32-34, 38-39, 82-88, 95-98 and 122-137 provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 8-12, 15-16, 18-22, 24-26, 34-39 and 40 of copending Application No. 09/458,813. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of 09/458,813 are drawn to a species of the genus of the instant claims.

Claim Rejections

Summary of pending and examined claims 1-98 and 122-137:

The claims are drawn to an isolated infectious chimeric parainfluenza virus (PIV) and immunogenic composition comprising N, P, L, and a partial or complete PIV background

genome or antigenome of PIV combined with one or more heterologous genes encoding an antigenic determinant of a heterologous pathogen. The heterologous genes can encode human PIV proteins such as N, P, C, D, V, M, F, HN and/or L proteins from HPIV1, HPIV2 or HPIV3. The glycoproteins of the PIV genome can be substituted for a counterpart gene in the other pathogen, particularly the HN and F proteins. A particular species claimed is PIV3 JS *cp*45 having attenuating mutations. Other pathogens can be combined such as measles (HA and F) and RSV (F and G) proteins.

Also claimed are HPIV genes (glycoproteins HN and/or F, or a segment encoding a cytoplasmic domain, transmembrane domain, ectodomain or immunogenic epitope thereof) that can be substituted for one or more counterpart genes or genome segments within the BPIV background genome or antigenome. BIV can also be incorporated to make a human-bovine chimeric PIV. Also claimed are specific amino acid substitutions that result in phenotypic changes and alter genes. Cytokines can be combined with the PIV.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

- Claims 1-25, 28-29, 32-34, 38-65, 74-77, 80-86, 90-91, 95-97, 122, 125-137 are rejected under 35 U.S.C. 102(e) as being anticipated by Belshe *et al* (5,869,036).

Belshe teaches an isolated cp-45 hybrid virus (a derivative of HPIV-3 JS) which is suitable for use as a vaccine in humans and animals comprising nucleic acid encoding nucleocapsid protein, phosphoprotein, at least one surface antigen of a target virus, and large polymerase protein (cols. 2-3). The target virus must have an envelope and one or more surface antigens or surface glycoproteins, such as HPIV-1, HPIV-2 and RSV. Belshe discloses that the gene sequence which encodes the surface glycoproteins of the target virus may be substituted for the corresponding sequence in the cp45 genome which codes for the HN and F proteins, to result in a chimeric genome (cols. 8-9).

Bovine RSV and cattle HPIV- are potential target viruses. Other viruses include RSV (F and G proteins), influenza, measles (HN and F protein), HIV and others (col. 8, lines 42-58). Attenuating mutations are introduced into the L segment as well as other proteins (col. 5, lines 42-67 and col. 6, lines 1-3). Belshe teaches that the cp45 genome has amino acid substitution at Leu992 in the L protein.

Belshe says the chimeric PIV can be used in a vaccine, or immunogenic composition, comprising a physiologically acceptable carrier (column 2, lines 32-33). Therefore, the claimed invention is anticipated by Belshe.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

- Claims 1-98 and 122-137 are rejected under 35 U.S.C. 103(a) as being unpatentable over Belshe *et al* in view of Collins *et al* (6,264,957) and Klein *et al* (WO93/14207).

  The teachings of Belshe are described above.

  Belshe is silent on:

  - rPIV3-2TM modified to incorporate attenuating mutations
  - glycoproteins fused to a cytoplasmic tail region
  - incorporating a cytokine
  - attenuating mutation at position 456 of the HPIV3 L protein
  - chimeric PIV is a subviral particle

However, Collins teaches RSV vaccines comprising subviral particles. One would have been motivated to modify the chimeric PIV of Belshe by substituting subviral particles because it was known in the art at the time of the invention that subviral particles are effective in vaccine compositions as taught by Collins. Also taught is the incorporation of cytokines, such as

members of interleukins (col. 11, lines 30-35). It would have been obvious to incorporate a gene of interest encoding an interleukin into the chimeric PIV of Belshe because Collins uses a similar chimeric. Further, one would have a reasonable expectation of success given the known functions of cytokines to elicit a greater immune response.

Klein teaches a multimeric hybrid gene, comprising RSV (G or F protein) and HPIV (F or HN protein), and combinations of these proteins such as F proteins from both PIV3 and RSV, see pages 36-37. Klein teaches a vaccine formulated for administration intranasally. One of ordinary skill would know the dosage required to elicit an immune response and would have been **motivated to make the modifications of dosage and administration in order to achieve the maximum immune response**. One would also know where to add the heterologous gene segment given the well-known art of recombination and would have been **motivated to incorporate the segment in such a way as to ensure its expression and stability**. Belshe teaches a method of incorporating the heterologous (target gene clone) segment by ligation into the PIV clone. One of ordinary skill would also have known where and how to make attenuating mutations; lacking evidence to the contrary, the mutation at position 456 has not been given patentable weight. Applicant is invited to point to the significance of a mutation of position 456. Stabilizing the mutation by making multiple nucleotide changes in a codon specifying the mutation is well with the capabilities of one of ordinary skill, and would have been advantageous in order to ensure expression of the mutation. One would have had a reasonable expectation of success given the well known practices of foreign gene expression. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

10. In anticipation of Applicant's arguments and for the sake of compact prosecution, the following potential arguments are addressed:

- Belshe's disclosure is non-enabled. Belshe is limited to a plasmid expressing a wtPIV3 L protein with a restrictive temperature and speculates that the L gene of cp45 possesses mutations that might be useful in a vaccine. Belshe fails to show cDNA constructs that produce wtPIV3 viruses or chimerics. Belshe fails to recover any virus from cDNA.
  - The Office's position is that Belshe describes a method for producing an attenuated hybrid/chimeric virus from a cDNA clone (cols. 9-10). One of skill would have had a reasonable expectation of success that Belshe's description (cols. 9-10) would have produced a hybrid/chimeric virus. Hoffman *et al.* (reference BM of IDS) show the construction and recovery of a full-length clone of HPIV-3 encoding a recombinant, infectious virus (pages 6-7). Therefore, at the time of Belshe's invention, methods of construction and isolation of recombinant, infectious PIV clones were known.
- Belshe's disclosure is unreliable. Belshe fails to disclose the nature of the attenuations *in vivo*. Not all attenuating mutations *in vitro* would be attenuated *in vivo*.
  - The Office notes that Applicants' claims are drawn to products only, not methods of making. Belshe fails to disclose the nature of the

attenuating mutations *in vivo*. Applicants are claiming *one* or more attenuating mutations and Belshe describes at least one attenuating mutation that is identical to Applicants' mutation. Therefore, the product of Belshe is expected to have the same attenuating features as Applicants' product.

Conclusion

11. No claim is allowed.

Papers relating to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 located in Crystal Mall 1. The Fax number for Art Unit 1648 is (703) 308-4426. All Group 1600 Fax machines will be available to receive transmissions 24 hrs/day, 7 days/wk. Please note that the faxing of such papers must conform with the Notice published in the Official Gazette, 1096 OG 30, (November 15, 1989).

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Stacy S. Brown, whose telephone number is (703) 308-2361. The Examiner can normally be reached on Monday through Friday and alternate Wednesdays from 6:30 AM-4:00 PM, (EST). If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's Supervisor, James C. Housel, can be reached at (703) 308-4027. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Stacy S. Brown
July 24, 2002

HANKYEL T. PARK, PH.D
PRIMARY EXAMINER